ACUTE ILEUS

COMPARISON OF TOXICITY OF OBSTRUCTED AND NON-OBSTRUCTED INTESTINAL CONTENTS

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PART I: QUALITATIVE

ACCEPTING the dictum that a poison was present in the obstructed intestine which could not be found in the unobstructed intestine, the experiments, the results of which are here reported, were begun in 1926. Their object was to ascertain whether or not, if such a poison did exist, there was any demonstrable time factor in its formation: in other words, whether the obstructed gut contents became more toxic the longer the obstruction lasted and, if so, how soon after obstruction they first began to be demonstrably toxic as tested by intravenous injection into other animals. If the results were positive, it was hoped that any definite time factor discovered might be used as a basis for rational recommendation regarding the possible use of enterostomy in human cases of acute ileus. A preliminary report[1] was published in 1927.

The published results of various investigators [2, 3, 4, 5, 6, 7, 8, 9,] up to that time were therein summarized as follows: "In obstructed intestines, the time factor for the formation of poison sufficient to cause marked sickness or death of the animal into which the content was injected (intravenously or intraperitoneally) has been found by different workers to vary from four hours to ten days." These variations noted appeared to depend partly upon (*a*) the level of obstruction; (*b*) the type of obstruction, whether simple or by closed loop; (*c*) whether there was or was not any serious trauma to the intestinal or mesenteric blood supply; (*d*) the preparation of the content for injection; (*e*) the amount used for injection; (*f*) the variety of the animal used in the experiment; and (*g*) individual differences of reaction in animals of the same kind.

The experiments herewith reported were undertaken specifically to determine whether any more definite information than this could be obtained in relation to the length of time required for the formation of poison. In order to avoid some of the presumable causes of variation in results (noted above) the following limitations were imposed:

(*a*) The intestine was obstructed at the same level in all cases (about 30 cm. from the duodenojejunal junction). This point of obstruction was used in all cases except the 12 hour group in which a point a little higher was selected by mistake.

(*b*) The technic of obstruction was as nearly as possible the same in every case.

(*c*) Similar care was used in every case to avoid injury to the mesenteric vessels.

(*d*) The animals were killed by anesthetic in the same way at the end of the fixed period for each hour group, and were autopsied immediately. The mucosa and intestinal contents were removed in the same way in every case (immediately upon death of animal) into a fixed amount (200 cc.) of boiling water and sterilized by boiling for approximately five minutes. The material thus secured was extracted and prepared for injection by the same technic in every case.

(*e*) The amount injected was in each case the residue extracted from the entire content and mucosa of the obstructed segment of one dog up to the pylorus. This extract concentrated in water varied from 10 to 18 cc. in bulk.

(*f*) The same variety of animal (dog) was used in every case.

There remained at least four variables that were not controlled by these standards:

(1) The actual amount of poison injected was unknown.
(2) The animals used for injection test were not all of equal weight.
(3) The animals injected differed somewhat in apparent physical condition.
(4) No constant could be assumed as to their individual reactability to the poison.

These variables are exceedingly important, for Ingvaldsen, A. O. Whipple, Bauman and Smith[10] showed that the dried extract of the ileus toxin was lethal to dogs injected intravenously in the amount of about 13 mg. to the kilo of body weight. The first two of the above variables could have been controlled but the last two could not. However, these variables (in addition to others) necessarily exist among cases of acute ileus in humans with which it was expected to compare the results of this experimental animal study. For this reason, in addition to the difficulty of procuring animals of exactly the same weight and because the technical process of securing the toxin in a dry refined state is long and difficult, these two controllable variables were left uncontrolled.

Method: Typical Experiment.—Through a median abdominal incision and with careful aseptic technic a presumably healthy dog under ether anesthesia had the jejunum tied off tightly by one-half inch cotton tape 30 cm. below level of duodenojejunal junction, except in the 12 hour obstruction group where (by mistake) the gut was ligated 30 cm. below pylorus, leaving a much shorter obstructed segment, care being taken not to injure the mesenteric vessels. The abdominal wound was closed, dressing applied and the animal returned to his cage. Water ad lib (but no food) was given after operation till death. The obstructed dog was killed by chloroform anesthesia

at the end of a predetermined interval after obstruction.* The abdomen was immediately opened and the intestine from pylorus to obstructed point 30 cm. below duodenojejunal junction removed. The content of this portion was squeezed into a beaker containing about 200 cc. of boiling water. The resected intestine was then split longitudinally, the mucosa was scraped off from the muscularis by the handle or back of a scalpel and transferred to the boiling water with the intestinal contents. Boiling was continued about five minutes and the contents of the beaker then transferred to a mason jar and removed to the Chemical Laboratory. The chemical treatment was that followed by Ingvaldsen, Whipple, Bauman and Smith.[10] The mixture was filtered through gauze and cotton and treated with five volumes of 95 per cent alcohol. The precipitate, dissolved in water, was boiled with 1 Gm. of magnesium sulfate, then filtered through paper and re-precipitated with five volumes of alcohol. The precipitate was dissolved in a small amount of water and dialyzed in a collodion sac against distilled water for five days with thymol used as a preservative. The neutral mixture, now free from magnesium sulphate, was centrifuged and the supernatant fluid removed, boiled with acetic acid for a few minutes, cooled and again centrifuged. The clear fluid again precipitated with alcohol was filtered and the precipitate dissolved in a small amount of water. The extract of the obstructed intestinal content and mucosa thus obtained† was sterilized by boiling and each specimen was tested as follows:

Under ether anesthesia in a presumably healthy dog, a small incision was made in left side of neck exposing left external jugular vein. Anterior wall of vein was picked up between fine toothed forceps and hypodermic needle introduced. The filtered, refined, sterilized intestinal extract (varying in bulk from 11 to 18 cc.) was slowly injected. The needle puncture was then closed by ligature, the wound in neck closed by suture and animal returned to cage for observation. They were observed at about hourly intervals for the first five or six hours following injection and after that not observed again till about 24 hours after injection. All dogs that died showed symptoms of severe toxemia, apparent discomfort, marked prostration, vomiting and purging which was frequently of blood tinged material, slow respirations, weak hind extremities. Every injected dog that died was autopsied as soon after death as practicable. There was found at autopsy in all cases the typical conjestion of intestinal mucosa often accompanied with mucosal hemorrhages, and bloody intestinal con-

* There were 5 hour-groups, of five or six dogs in each, as follows: Five 72 hour obstruction; five 48 hour obstruction; six 36 hour obstruction; six 24 hour obstruction (2 groups); six 12 hour obstruction.

† The amount varied between 11 cc. and 18 cc. in different instances. The color varied from watery opalescent to greenish or brownish and in some cases there was a small sediment at the bottom of the test tube. Experience showed that the color and sediment did not appear to indicate in any way the relative toxicity of the fluid.

tents which is apparently a characteristic effect of obstructed intestinal content poisoning.

The results of the tests may be tabulated as follows:

GROUP A

Adult Dogs — 72-Hour Obstruction

Serial No. obstructed dog	Serial No. injected dog	Amount of fluid injected	Results
8240	8315	10 cc.	Slight toxemia. Recovery complete in 24 hrs.
8352	8413	15 cc.	Severe toxemia. Recovery after 24 hrs.
8269	8414	15 cc.	Very severe toxemia. Dead in 2¾ hrs.
8326	8415	18 cc.	Severe toxemia. Recovery after 24 hrs.
8358	8416	17 cc.	Severe toxemia. Dead in 6 to 24 hrs.

GROUP B

Adult Dogs — 48-Hour Obstruction

8386	8547	10 cc.	Severe toxemia. Recovery after 48 hrs.
8359	8548	17 cc.	Severe toxemia. Recovery after 48 hrs.
8487	8549	14 cc.	Severe toxemia. Recovery after 48 hrs.
8447	8550	16 cc.	Severe toxemia. Dead in 5 hrs.
8430	8551	16 cc.	Severe toxemia. Dead in 6 to 19 hrs.

GROUP C

Adult Dogs — 36-Hour Obstruction

8704	8773	14 cc.	Severe toxemia. Recovery after 24 hrs.
8714	8774	13 cc.	Severe toxemia. Dead in 10 to 23 hrs.
8717	8775	15 cc.	Moderate toxemia. Recovery after 24 hrs.
8723	8776	15 cc.	Moderate toxemia. Recovery in 24 hrs.
8730	8777	14 cc.	Slight toxemia. Recovery in 24 hrs.
8735	8778	16 cc.	Severe toxemia. Dead in 4½ hrs.

GROUP D

Young Puppies — 24-Hour Obstruction

8826	8858	7 cc.	Moderate toxemia. Recovery within 24 hrs.
8827	8859	6 cc.	Severe toxemia. Dead within 2½ hrs.
8828	8860	6 cc.	Severe toxemia. Dead within 3½ hrs.
8829	8861	8 cc.	Severe toxemia. Dead within 3¼ hrs.
8830	8862	6 cc.	Severe toxemia. Dead within 3 hrs.
8831	8863	7 cc.	Severe toxemia. Dead within 3½ hrs.

Following our original hypothesis, it had been expected that the 24 hour obstruction contents would show less toxic power than that of the 36 hour, 48 hour and 72 hour groups. For that reason puppies, instead

of adult dogs, were chosen as they were believed to be more susceptible, just as children are apparently more susceptible to intestinal disturbances than are adults: the injection of the intestinal content into a vein being held to represent a situation similar to its rapid absorption from the intestinal mucosa via its lymphatics and veins. The 24 hour obstruction poison when tested in puppies was, however, apparently so much more deadly than the longer obstruction poison that we were led to question the validity of the results as a fair comparison with the other hour groups. The test was, therefore, repeated, every factor being similar except that adult dogs were used for the injection as in the other hour groups. The results are tabulated below.

GROUP E

Adult Dogs — 24-Hour Obstruction

Serial No. obstructed dog	Serial No. injected dog	Amount of fluid injected	Results
9355	9397	10 cc.	Very slight toxemia. Rapid recovery.
9356	9398	12 cc.	Very slight toxemia. Rapid recovery.
9357	9399	12 cc.	Moderate toxemia. Found dead after 24 hrs. Pneumonia.
9358	9400	10 cc.	Very slight toxemia. Rapid recovery.
9359	9401	11 cc.	Slight toxemia. Rapid recovery.
9360	9402	10 cc.	Very slight toxemia. Rapid recovery.

The results in this second group of 24 hour obstruction were so different from the results in the first 24 hour group that we decided to try a 12 hour obstruction group. The results of this experiment are tabulated below.

GROUP F

Adult Dogs — 12-Hour Obstruction

Serial No. obstructed dog	Serial No. injected dog	Amount of fluid injected	Results
9095	9154	12 cc.	Very slight toxemia. Rapid recovery.
9096	9155	10 cc.	Severe toxemia. Dead in 5 to 8 hrs.
9097	9156	12 cc.	Very slight toxemia. Rapid recovery.
9098	9157	11 cc.	Very slight toxemia. Rapid recovery.
9099	9158	11 cc.	Very slight toxemia. Rapid recovery.
9100	9159	10 cc.	Very slight toxemia. Rapid recovery.

The fact that there were deaths in the early obstruction as well as in the late obstruction groups led us to question whether we had been justified in our original assumption that there was a poison in the obstructed intestine which could not be demonstrated in the non-obstructed intestine. We therefore decided to test by injection the toxicity of material from non-obstructed intestines obtained, refined, and injected in exactly the same way as the content of obstructed intestines had been. The results are tabulated below.

GROUP G

Adult Dogs — Non-Obstructed Control

Serial No. non-obstructed dog	Serial No. injected dog	Amount of fluid injected	Results
9657	9775	about 10 cc.	Severe toxemia. Dead in 4 hrs.
9653	9776	13 cc.	Apparently recovering from toxemia after 4 hrs. but found dead 24 hrs. later.
9656	9777	11 cc.	Severe toxemia. Dead in 3 hrs.
9652	9778	11 cc.	No toxemia, apparently.
9655	9779	12 cc.	Very slight toxemia. Rapid recovery.

The death of three out of five dogs in this GROUP G (following injection of the extract of non-obstructed intestine) made it appear that there was actually present in the non-obstructed intestine a poison similar to that found in the obstructed intestine. Moreover, at autopsy, two out of the three dead dogs had the bright red congestion of the small intestine mucosa (most marked in the duodenum and fading toward the ileum) together with blood-tinged contents that we have previously associated only with the fatal toxemia following injection of obstructed intestinal contents. Findings in the third dead dog were suggestive but not convincing of the same pathology. It, therefore, seemed impossible to retain our original assumption that there was no similar poison in the non-obstructed intestine. This conclusion appears more inevitable if we summarize the results which have been tabulated above for the individual groups and contrast them with each other. A summary of the results (tabulated in individual groups above) is shown below.

Summary of Results of Toxicity Tests of Various Obstructed and Non-Obstructed Contents

Group	No. of dogs	No. died	Mortality per cent of group	Remarks
72-hr. obstruction	5	2	40	All adult dogs.
48-hr. obstruction	5	2	40	All adult dogs.
36-hr. obstruction	6	2	33⅓	All adult dogs.
24-hr. obstruction	6	5	83⅓	All young puppies. May have extra susceptibility.
24-hr. obstruction	6	1	16⅔	All adult dogs.
12-hr. obstruction	6	1	16⅔	All adult dogs.
Non-obstructed	5	3	60	All adult dogs.

This summary shows two striking features: the high mortality of the group of puppies injected with 24 hour obstruction fluid and the high mortality of dogs injected with non-obstructed intestine contents. Ignoring these two groups for the moment the above summary seems to indicate an increase in the toxicity of the obstructed contents with the longer periods of obstruction. But the two striking groups cannot be ignored. They must either be satisfactorily explained or it must be admitted that the original

assumption (poison present in obstructed contents but not in normal contents) is invalid and that the object of the experiments (to ascertain at what period—after onset of obstruction—poison becomes demonstrably present in the intestine) was unattainable.

If we had not used the puppies among the test animals and if we had not tested the toxicity of the non-obstructed contents, our results would have been apparently satisfactory, logically to be expected and rather convincing. But they would have been fallacious.

SUMMARY OF PART I

The results of this first group of experiments (designed to discover whether or not the contents of the obstructed intestine became demonstrably more toxic with the increase in the obstruction time) were inconclusive: first, because the test of the 24 hour material, on puppies, made it appear more toxic than the 36 hour, the 48 hour or the 72 hour material; and secondly, because the non-obstructed material appeared to be more toxic than the obstructed material.

It might be plausibly argued that the puppies tested were more susceptible than adult dogs and that, because of their small size, they received relatively larger dosage of the material than did the adult dogs. This argument could be supported by the fact that, when adult dogs were tested with similar (24 hour) material, they appeared to be—on a mortality percentage basis—five times more resistant than the puppies.

As regards the non-obstructed control tests, it might be argued that some of the apparently normal dogs, from which the non-obstructed intestines were taken, really had distemper with no other sign of it than the slightly congested mucosa which was noticed in two or three of them. The non-obstructed intestinal contents of dogs suffering from distemper have been shown by Ellis[20] to be decidedly toxic. All we can say, in this regard, is that—if they had distemper—the signs were too obscure for us to recognize and we considered these dogs to be healthy.

If now we should ignore the result of the test on the group of puppies (which would seem almost justifiable) and in the non-obstructed control group (which would not seem justifiable) it would appear that the first group of experiments indicated an increasing toxicity with the increase in length of obstruction time (based on an increasing percentage of mortality in the injection tests).

We do not, however, believe that this appearance is reliable. It seems rather to be fallacious, particularly when viewed in the light of the results of the second group of experiments (whose report follows) which were designed to compare quantitatively the relative toxicity of obstructed and non-obstructed contents. But even in the light of these qualitative tests, we believe the non-obstructed contents to be toxic.

PART II: QUANTITATIVE

On the assumption that there was poison present in non-obstructed intestine, the question arose as to whether it existed in amounts at all similar to those found in the obstructed intestine.

Ingvaldsen, A. O. Whipple, Bauman, and Smith,[10] in 1923, secured 1 Gm. of dry toxic substance from the obstructed intestine of 14 dogs, using a method of chemical extraction similar to that described by Ellis but with additional steps to further purification. Seventy-one mg. of this toxic substance dissolved in water and injected intravenously into a dog weighing 5½ kilos (13 mg. to the kilo) resulted in a characteristic toxemia and in his death in 2¾ hours. Autopsy showed the characteristic intestinal pathology of intense mucosal irritation.

In 1928, we killed by chloroform five presumably healthy dogs and removed into boiling water the contents and mucosa of nearly the entire small intestines. Through the kindness of Dr. Edgar G. Miller, this was treated in the Department of Biochemistry by exactly the same method of extraction and purification which Ingvaldsen and collaborators had reported in the case of obstructed contents. The dry substance thus secured weighed 186 mg. It was of dirty white color, chalky consistency and when dissolved in water made a cloudy, opalescent solution. Two apparently healthy dogs were selected and the toxin, dissolved in water and freshly sterilized by boiling, was slowly injected into the external jugular vein exactly as in the previous experiments. The results are tabulated below.

GROUP H

Adult Dogs — Non-Obstructed Controls

Serial No. injected dog	Weight of dog	Weight of dried extract	No. of mg. per kilo	Results
9972	5.9 Kg.	75 mg. in 7.5 cc. water	12.7	Vomiting and purging and marked depression. Moribund in 8 hrs. Found dead next day. Pneumonia.
9973	6.1 Kg.	90 mg. in 9 cc. water	14.7	No vomiting or purging. Moderate depression. Almost completely recovered at end of 8 hrs.

There are two interesting points of contrast here indicated between the contents and mucosa of obstructed and non-obstructed intestine: (1) The amount of dried extract obtainable (using the same chemical method); and (2) its effect when injected intravenously.

From the obstructed intestine of 14 dogs was obtained 1,000 mg. of dried extract, an average of 71 mg. per animal. From the non-obstructed intestine of five dogs was obtained 186 mg. of dried extract, an average of 37 mg. per animal. When injected intravenously (in approximately the same amount of mg. per kilo of body weight) the obstructed extract killed a dog in 2¾ hours with autopsy findings typical of acute ileus poisoning. The non-

obstructed extract had very slight apparently toxic effect on one dog and, when tested on another, showed only moderate effect within four hours and, although this latter dog was found dead the next day there were no characteristic pathologic findings as in acute ileus poisoning and there was an early pneumonia of one lung which probably contributed to its death. These observations were so much at variance with those in GROUP G, where the less refined non-obstructed contents accounted for a 60 per cent mortality of injected dogs, that it seemed worthwhile to persist in the attempt to compare quantitatively the toxic effect of obstructed and non-obstructed contents.

In 1935, therefore, a group of 13 non-obstructed, apparently relatively normal dogs were killed by chloroform, the small intestinal contents and mucosa from pylorus to cecum were removed and treated by the same method used in 1924 by Ingvaldsen, A. O. Whipple, Bauman and Smith.[10] The chemical work was done in the chemical laboratory of the Department of Surgery at the College of Physicians and Surgeons by Miss Hamlin under the direction of Dr. Louis Bauman. Nine hundred and twenty mg. of dry residue was secured by this method from 13 non-obstructed dogs as compared with 1,000 mg. obtained from 14 obstructed dogs in 1924. This dried residue was dissolved in 92 cc. of 0.9 per cent sterile Na Cl solution (10 mg. to 1 cc. of solution) and, being found slightly acid, was neutralized to phenolphthalein by adding a little sodium carbonate. The resulting solution was without precipitate, almost water-clear and colorless. The toxicity of the material was tested by injection into the external jugular vein of presumably healthy adult dogs, exactly as in the earlier experiments. The following table shows the amount injected and the results observed.

GROUP J

Adult Dogs — Non-Obstructed Controls

Serial No. injected dog	Weight of dog	Weight of dry extract	No. of mg. per kilo	Results observed
12825	14.7 Kg.	147 mg.	10.0	No sign of toxemia except slight depression.
12829	4.9 Kg.	70 mg.	14.3	Severe toxemia. Vomiting and purging. Recovered in about 6 hrs.
12826	14.0 Kg.	210 mg.	15.0	Moderate toxemia. Purging and depression. Recovery after 6 hrs.
12827	13.1 Kg.	209 mg.	16.0	Vomiting, purging, coma. Death in 2½ hrs. Characteristic autopsy findings.
12828	12.7 Kg.	216 mg.	17.0	Severe toxemia. Vomiting. Bloody stools. Recovery after 24 hrs.

Reviewing the results, it seems impossible to deny that this material, obtained from the non-obstructed intestines of apparently healthy dogs, is toxic. Bearing in mind the fact that it was obtained by exactly the same method of

chemical extraction which had been used by Invaldsen, Whipple, Bauman and Smith, in the obstructed intestine; added to the fact that, when injected into dogs, in the same way and in about the same amount as the obstruction poison, it gave rise to similar symptoms, one is inclined to believe that its toxicity may be due to similar (if not the same) factors as in obstruction poison. It is possible, of course, that the poison may be the same as obstruction poison, but we have no evidence to justify such an assumption, because we made no chemical analysis of the non-obstructed extract.

One does not know whether the poison extract resides originally in the intestinal contents or in the mucosa. In the case of these non-obstructed dogs, it would appear to be in the mucosa. For the total contents recovered from the non-obstructed intestines of 13 dogs was only about 20 cc. of fluid and the usual worms. There was, however, roughly about three times as much mucosa taken by us from the non-obstructed intestines as was taken by Ingvaldsen, Whipple, Bauman and Smith from the obstructed intestines for chemical extraction. The entire small intestine was used in the former case, and only the obstructed segment in the latter. The contents of the obstructed intestines was, however, far greater than that of the non-obstructed intestine.

In both instances (obstructed and non-obstructed) approximately the same amount of extract was secured, in a dried to constant weight form. An average of 71.4 mg. was recovered from each of the obstructed dogs and an average of 70.8 mg. from each of the non-obstructed. Taking into consideration the fact that there was more contents and less mucosa in the obstructed dogs, it seems possible that the poisonous extract may have resided largely in the contents. In the case of the non-obstructed dogs, however, there was so great a preponderance of mucosa over contents that it seems probable the mucosa was largely the source of the extract.

Collecting the results, both qualitative and quantitative, of the toxicity tests and dividing them into two groups, Obstruction Extract and Non-Obstruction Extract, we may tabulate them as follows:

Comparative Toxicity of

Obstruction Extract		*Non-Obstruction Extract*	
No. of specs. tested	34	No. of specs. tested	12
No. producing symptoms	34	No. producing symptoms	11
No. resulting in death	13	No. resulting in death	5
Confirmed by autopsy	13	Confirmed by autopsy	4
Mortality rate 38.2%		Mortality rate 41.7%	

SUMMARY OF PART II

The second group of experiments (designed to test the toxicity of non-obstructed intestinal contents and mucosa and to compare the amount of poison and its degree of toxicity with that found in the obstructed intestine) were more convincing in their results. From them it appeared:

(1) That there is a toxic substance in the non-obstructed intestine whose action, when tested by injection, is similar to that of the so called obstruction poison.

(2) That, when quantitatively tested, it appears to be about as toxic as the obstruction poison.

(3) That (judging by the amount of mucosa used for the extraction and the amount of extract secured, in the obstructed and non-obstructed groups) the poison exists in smaller amounts in the non-obstructed than in the obstructed intestine. If these appearances are accepted as valid representation of the facts (and we are inclined to accept them as such) they argue against the commonly held conception of obstruction toxemia: that is as being due to a peculiar obstruction poison formed only after the onset of obstruction. They tend to suggest rather the prior existence of a poison in the non-obstructed intestine which, after the onset of obstruction, is collected there in larger amounts, due to the lowered absorption from an obstructed intestine and to the impossibility of discharging it through the normal channel. They tend similarly to strengthen the claims of those who argue that the normal uninjured mucosa does not allow to pass into the lymphatics and blood vessels poisons which are apparently able to pass through the mucosa after it has been injured sufficiently to interfere with its integrity as a protective agent.

DISCUSSION

From these collected observations, therefore, one gets the impression that there is little difference, qualitatively and quantitatively, between the toxicity (intravenously injected) of the extract from obstructed and non-obstructed intestinal contents in dogs. The observations reported herein are, however, too few to carry much weight by themselves and confirmatory evidence must be sought to reinforce the impression that they give. Such confirmation may be found in the reports of work done by Kukula,[6] Charrin,[12] Bouchard,[11] Magnus-Alsleben,[13] Roger and Garnier,[14] Falloise,[15] Cybulski and Tarchanoff,[16] Braun and Boruttau,[17] Davis, D. M.,[18] Wangensteen and Chunn.[19]

Bouchard, in 1887, tested the watery (also alcohol and ether) extracts of non-obstructed intestines by injection into animals and reported them to be toxic.

Kukula, in 1901, investigating normal intestinal contents, found toxic substances and classed them as (a) breakdown products of carbohydrates and (b) putrefaction products of proteins.

Charrin, in 1904, stated that, in its non-obstructed condition the intestinal contents are poisonous.

Magnus-Alsleben, in 1904–1905, said that a toxic substance existed in non-obstructed, upper small intestine contents and mucosa after feeding various kinds of meat and apparently also after bread, fats and starches.

Roger and Garnier, in 1905–1908, tested by injection the toxicity of gastric, small intestine and colon contents of non-obstructed intestine. They

used dogs and rabbits and reported that the contents of the small intestine were more toxic than gastric or colon contents. Their conclusion regarding the non-obstructed contents was that it was remarkable for the constancy of its toxicity and for the consistency of its toxic dosage. Then, comparing the toxic dosage of obstructed small intestine content with that of the non-obstructed, they reported that the latter was rather more poisonous than the former. They precipitated the obstructed contents with alcohol and found the precipitate (dissolved and injected in water) very fatal while the filtrate was only mildly toxic. Their final conclusion regarding the relative toxicity of obstructed and non-obstructed contents was that occlusion of the intestine (obstruction) in dogs lessens the toxicity of its contents below that of normal contents.

Falloise, in 1907, made a careful study of the various products of digestion found in the intestine of the human and of certain animals. He stated that the normal contents of human intestine was toxic for dogs and rabbits (as tested by injection into vein) and that normal contents of these animals were also toxic for the same animals. He studied only the non-obstructed contents believing that the obstructed contents were abnormally conditioned. He sterilized the watery extract of intestinal contents by tyndallization (repeated to 55° C.) and his experimental work was carefully planned and executed. His deductions were thoughtfully made and are highly convincing. He recorded accurately the symptoms produced by the injections. The most striking and consistent symptoms were (1) rapid fall of blood pressure, (2) severe dyspnea, (3) incoagulability of the blood, and (4) hypoleukocytosis. He said that the severity of the symptoms and their rapidity of onset appeared to depend upon (*a*) the amount injected, (*b*) the speed of injection, and (*c*) the individual resistence of the dog tested. His final conclusion was that normal, non-obstructed contents were toxic and that the toxicity probably came from products of digestion in the small intestine as the contents of this were more poisonous than those of large intestines.

Cybulski and Tarchanoff, in 1907, repeated enough of Falloise's experiments to confirm his results. But they differed from his deduction that the toxicity of normal intestinal contents was due to digestive products. They claimed that the toxicity was due to the digestive ferments and particularly to the pancreatic juice.

Their final conclusion was that normal intestine contents were toxic but that the toxicity was due largely to the presence of pancreatic juice; because, by injecting the latter alone, they secured results almost entirely similar to those of Falloise's injections with small intestine contents.

Brown and Boruttau, in 1908, after numerous obstruction experiments on dogs and cats, undertook a similar research on apes. They called attention, in their report, to the fact that several previous investigations had claimed that obstructed contents were more toxic than normal contents. Brown and Borut-

tau, however, felt that the methods used had not been sufficiently exact to make such claims convincing.

They themselves had found that, in certain injection experiments, using equal amounts of obstructed and of non-obstructed contents, the latter was sometimes lethal and the former was not. They did not, apparently, as Roger and Garnier had, test quantitatively with any exactness the relative toxicity of obstructed and non-obstructed contents. However, they secured the strong impression that obstructed contents may be no more toxic than normal contents. They found that absorption from the intestine was slowed down by obstruction conditions. In general, they agreed with the work of Roger and Garnier and of Falloise. Finally, they concluded that there was no demonstrable proof of a special obstruction poison and that the normal intestinal contents were rather more toxic than the obstructed contents. Moreover, they held that absorption from an obstructed intestine was so greatly slowed down that in some cases the presence of a lethal dose of strychnine in the obstructed gut failed to cause strychnine poisoning.

Davis, in 1914 found the normal intestinal contents of dogs, containing the ordinary food residues, fatally toxic when injected intravenously into other dogs. He also made fistulae in dogs 35 cm. below the pylorus and tied off or dissected away the pancreatic and bile duct so that no bile or pancreatic juice could enter the gut. Fluid syphoned from these fistulae, when injected intravenously into other dogs, had, in all cases, effects identical with those caused by injection of closed loop fluid. He accepted this as evidence that normal small intestine secretion without the presence of bile or pancreatic juice was quite definitely toxic.

Wangensteen and Chunn, in 1928, compared the toxicity of obstructed and normal intestinal contents, using dogs. They used contents only, apparently, and no mucosa. The normal contents were expressed (after killing the animal) from the whole of the small intestine. The contents of obstructed dogs (after two or three days obstruction) were expressed separately from above and from below the point of obstruction and tested separately. The contents were filtered (under suction) until clear, often colorless and sterile. The amount injected was usually about 15 cc. The normal contents were injected into seven dogs with mortality of 28.6 per cent. The obstructed contents were injected into ten dogs with no mortality. They then tested on rats the normal and obstructed contents of dogs. The normal contents (injected intraperitoneally) gave a 7.7 per cent mortality; the obstructed contents (from above the obstruction) gave a 9.9 per cent mortality and the contents from below the obstruction gave a 75 per cent mortality. Normal contents of rabbits' intestine injected into rats (intra-peritoneally) gave 33.3 per cent mortality and obstructed contents gave a 20 per cent mortality.

Their conclusions were that all intestinal contents were toxic on injection; furthermore, that the contents of non-obstructed dog or rabbit when injected

gave rise to the same symptoms as obstructed contents and were just as toxic.

Taking these reports collectively, we have here a considerable weight of evidence in favor of a definite poison or poisons existing in the contents and mucosa of the normal, non-obstructed small intestine: a poison which when injected intravenously gives rise to symptoms similar to those caused by the injection of obstructed contents.

If this evidence be accepted as valid it would seem hardly profitable to look any longer for a specific obstruction poison; an acute ileus toxin. For, if similar poisons are present in the intestine before and after obstruction, the vital question is not how and why they are formed but rather how and why they are absorbed, in lethal dosage, after obstruction and not before.

REFERENCES

[1] vanBeuren, F. T., Jr., *et al.*: Am. Jour. Surg., New Series, vol. 1, p. 284, November, 1926.

[2] Whipple, G. H., Stone, and Bernheim: Jour. Exp. Med., vol. 17, p. 307, 1913; idem, vol. 19, p. 144, 1914; Bull. Johns Hopkins Hosp., vol. 23, p. 159, 1912.

[3] Murphy and Brooks: Arch. Int. Med., vol. 15, p. 392, 1915.

[4] Dragstedt, *et al.*: Am. Jour. Physiol., vol. 46, p. 366, 1918; Proc. Soc. Exp. Biol. & Med., vol. 14, p. 17, 1916–1917.

[5] Murphy and Vincent: Boston Med. and Surg. Jour., vol. 165, p. 684, 1911.

[6] Kukula: Arch. für klin. Chir., vol. 63, p. 773, 1901.

[7] Von Albeck: Arch. für klin. Chir., vol. 65, p. 569, 1901.

[8] Clairmont and Ranzi: Arch. für klin. Chir., vol. 73, p. 696, 1904.

[9] Sugito: Mitt. a.d. Med. Fakult. d.k. Univ. Zu Tokyo, vol. 31, p. 117, 1924; also M. a.d.M.F. d.k. Univ. Kyusha Fukuoka, vol. 9, p. 229.

[10] Ingvaldsen, Whipple, A. O., Bauman and Smith: Jour. Exp. Med., vol. 34, No. 1, p. 117, January 1, 1924.

[11] Bouchard: Lecons sur l'autointoxications, Paris, 1887; Lectures on Auto-intoxication in Disease, Philadelphia, 1906, tr. French ed. 1887.

[12] Charrin: Sem. Med., vol. 24, p. 377, 1904.

[13] Magnus-Alsleben: Hoffmeisters Beiträge, vol. 6, p. 503, 1904–1905.

[14] Roger and Garnier: Comptes Rend., vol. 59, pp. 388, 674, 677, 1905; vol. 64, pp. 426, 610, 83, 1908; vol. 65, pp. 202, 389, 1908; Rev. de Med., vol. 26, p. 953, 1906.

[15] Falloise: Archive Internat. de Physiologie, vol. 5, p. 159, 1907.

[16] Cybulski and Tarchanoff: Archiv. Internat. de Physiologie, vol. 5, p. 257, 1907.

[17] Braun and Boruttau: Deutsch. Ztschr. für Chir., vol. 96, p. 544, 1908.

[18] Davis, D. M.: Bull. Johns Hopkins Hosp., vol. 25, p. 33, 1914.

[19] Wangensteen and Chunn: Arch. Surg., vol. 16, p. 606, 1928.

[20] Ellis: ANNALS OF SURGERY, vol. 75, p. 429, 1922.